STATEMENT OF
THE AMERICAN CHEMISTRY COUNCIL

Hearing on Safety of Phthalates and Bisphenol-A in Everyday Consumer Products
House Committee on Energy and Commerce
Subcommittee on Commerce, Trade, and Consumer Protection
June 10, 2008

## SUMMARY OF ACC'S POSITION

The American Chemistry Council represents the leading business of chemistry. Products supplied by the chemistry sector are essential in manufacturing, agriculture, energy, transportation, technology, communications, health, education, defense, and virtually every aspect of our lives. Basic industrial chemicals are the raw materials for thousands of other products including plastics, water treatment chemicals, detergents, pharmaceuticals and agricultural chemicals. These applications include medicines and medical technologies that save lives, computers that expand our horizons, foods we eat, water we drink, cars we drive, homes in which we live, and clothes we wear.

We understand that recent media attention has created public concern and confusion about some of these chemicals – a family of compounds called phthalate esters, and another compound called bisphenol A. We are pleased to present this testimony to help address some of the confusion.

**Bisphenol A** is a single compound used primarily to make polycarbonate plastic and epoxy resins. It is also used to make resins used as dental sealants and composites. Only trace levels of residual bisphenol A remain in these materials and in consumer products made from these materials.

**Phthalate esters** describe a family of compounds used in many applications. The largest use is as an additive to plasticize, or soften, polyvinyl chloride. Before the addition of a plasticizer, polyvinyl chloride (vinyl) is actually a hard plastic.

These materials have been in use for decades. They have been subjected to extensive study worldwide, including by independent researchers as well as government agencies, and scientific review is ongoing. U.S. regulatory agencies charged with regulating these compounds in various applications, after reviewing the large body of scientific data, have reached conclusions supporting their safe use in important applications. The scientific evidence supports the continued use of these important materials.

## SCIENTIFIC EVIDENCE SHOWS THE PUBLIC NEED NOT BE CONCERNED ABOUT PRODUCTS CONTAINING PHTHALATES

Phthalates are primarily used to make vinyl soft and flexible. Flexible vinyl products are used in our cars, homes and workplaces and in hospitals to help save lives. These phthalates : diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), di-n-octyl phthalate (DnOP), di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP). For instance, BBP is most commonly used in flooring and insulating sealants. DBP is used in adhesives as a solvent for organic compounds and in cosmetics and personal care products. And DEHP is used in medical devices and other vinyl products.

Numerous government risk assessments have demonstrated that exposure to phthalates in toys and children's products generally pose no significant risk to children. Both the U.S. National Toxicology Program (NTP) and the European Union (EU) have performed risk assessments on phthalates, and have generally found no significant risk to children from exposure to these phthalates.[1] For example,

- For BBP, the NTP assessment found "***minimal concern for adverse developmental effects in fetuses and children***" and the EU assessment, which looked at all sources of exposure to children, including toys, found "***no concern for local exposure to BBP***" and "***no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.***" The EU assessment, to be thorough, considered the "unintentional use" of BBP in toys. Even with such use, the EU found no "***no need for further information or testing or risk reduction measures***" to protect consumers, including children.

- For DBP, the NTP assessment found "***minimal concern***" for fetal developmental effects for pregnant women with typical exposure, and "***some concern***" for male fetal development in women with high exposure, though this conclusion was based on exposure estimates that are significantly higher than actual exposures as measured by the CDC.

[1] The NTP's assessments can be found at: http://cerhr.niehs.nih.gov/reports/index.html; the EU assessments are available at: http://www.phthalates.com/RAs.

- For DEHP, the only concerns noted by the NTP for children were from very high exposures of infants or mothers undergoing intensive medical treatments, and "***some concern***" for children older than one year, based on very high assumed exposures from all sources. The EU assessment also expressed some concern for exposures to children. Again, however, DEHP is not used in the manufacture of children's articles that are intended to be mouthed, and the actual risk from exposure to other products is very low.

The European Chemicals Bureau, which managed the risk assessments performed by the EU member states, provided a draft conclusion of the exhaustive safety reviews of the principal phthalate (DINP) used in toys. It stated it was "unlikely to pose a risk" even for newborns. Regrettably, despite the vote of confidence by the Bureau, the European parliament had already moved forward with banning phthalates from some children's products. It was a decision based on politics, not sound science; a mistake that we hope not to see repeated in the United States.

The most relevant government risk assessment with respect to phthalates in toys is the U.S. Consumer Product Safety Commission (CPSC)'s 2001 safety assessment of vinyl toys softened with phthalates, in particular the phthalate that is by far most commonly used in toys – DINP.[2] This extensive risk assessment found "***no demonstrated health risk***" to children from exposure to DINP from toys and child care articles. The CPSC declined to take action on a petition to ban the use of phthalates in children's toys following its intensive review, which had included evaluation of children's behavior in mouthing toys.

Similarly, the NTP risk assessment of DINP found "***minimal concern***" for adverse effects on human reproduction or fetal development and for developmental effects in children. The EU assessment of DINP concluded that exposure to DINP from toys and baby equipment is "unlikely to pose a risk" for infants and newborns and that such exposure "is not considered of concern."

Besides CPSC and NTP, the U.S. Centers for Disease Control and Prevention (CDC) has also tested thousands of Americans for evidence of exposure to phthalates. The CDC data shows that average human exposure is far below

[2] The CPSC risk assessment package is available at: http://www.cpsc.gov/library/foia/foia02/brief/briefing.html. This URL links to CPSC briefing packages for Fiscal Year 2002. The first seven links on that page are the complete staff briefing package on PVC/DINP.

levels set by the U.S. Environmental Protection Agency (EPA) as protective of human health and that exposure levels are actually declining. Furthermore, the FDA, which regulates medical devices, has said that phthalate-softened devices have been used for years "without apparent ill effect."

In regards to the media attention around this issue, we have seen a number of major news outlets report that phthalates are "toxic and can cause reproductive problems in humans."

- Senator Dianne Feinstein in a press release issued on March 4th claimed phthalates can "interfere with the natural functioning of the hormone system" and "cause reproductive abnormalities and result in an early onset of puberty" in young children. There is no evidence that any phthalate has ever caused any of these effects in young children.
- A PBS report on March 21st by Senior Correspondent Maria Hinojosa said "phthalates help make … teething rings soft and pliable" and that "scientific evidence suggests that exposure to phthalates… may interfere with the sexual development of boys." First of all, phthalates are not used in the manufacture of these products – that is a myth. Furthermore, as stated above, there is no evidence that any phthalate can interfere with the sexual development of boys.
- An Associated Press story on April 8th stated that phthalates are "widely used in such products as baby bottles and teething rings." Again, false information.
- A Los Angeles Times story on April 27th labeled phthalates as plasticizers that are "often found in personal hygiene products that might alter children's hormones." This is a speculative statement that is not supported by the facts, as indicated above.

These statements are simply not true. Phthalates are not used in the manufacture of teething rings or baby bottles, a misinformation propagated by many of these news reports. Furthermore, to imply that phthalates are somewhat responsible for cancer, hormonal disruption or early puberty in children and for reproductive problems in adults also misinforms the public about the true nature of phthalates. While studies in animals have shown effects, actual studies of humans where volunteers were intentionally exposed or where critically ill infants were

exposed to high levels have FAILED to show any of these effects. What gets referenced over-and-over again are a handful of statistical correlations that have not been recognized as demonstrating real cause and effect.

It is unfortunate that these media reports referred to a handful of studies that attempt to link phthalate exposure to adverse health effects. Many of the studies are biased in their design, test only a small sample size or have uncontrollable variables. Other studies ignore or exaggerate real world human exposure or fail to register species differences. Some of these studies are also based on findings in rodents at extremely high exposure levels. Similar studies in primates at similarly high levels do not show these same effects. There is no evidence that these effects have ever occurred in humans.

In today's world, zero exposure to anything is impossible, and with today's advanced analytical techniques, incredibly tiny amounts can be measured. These levels do not necessarily constitute a health risk.

Some of these studies also rely heavily on statistics to demonstrate a correlation, but they cannot prove cause and effect and are often in immediate conflict with government agencies' findings. A recent example is a study led by Shanna Swan of the University of Rochester[3] which claims that the data collected from 85 infant boys and their mothers supports the hypothesis that prenatal phthalate exposure at environmental levels can adversely affect male reproductive development in humans. However, closer scrutiny reveals a number of significant flaws in the study's methodology:

- No adverse effects were detected in this study. This study provides no evidence that reproductive health or fertility of boys are affected by phthalates.
- Although the abstract reported finding a relationship between exposure and anogential distance, the details indicate no such relationship was found. Only after mathematically manipulating the distance measurement to an index was any relationship projected.
- The measurement of anogenital distance is of no known significance in the practice of medicine and has never been related to any reproductive problem in humans.

[3] The Swan study is available at http://www.shswan.com/articles/uploads/45/Swan_2005_Phthalate_AGD.pdf

- Twenty percent of the infant boys were dropped from the study because reliable measurement could not be obtained.
- Conversion of anogenital distance to anogenital index was done incorrectly. Anogenital distance does change with weight and age but the changes are not linear.
- No correction was made for height or premature births when converting anogenital distance to index.
- The single urine samples collected from 85 pregnant women were neither reliable nor valid since they were not adjusted for variable fluid intake, time of day, or other standard procedures. Nor were they taken at a standard time during gestation.
- The researchers used the wrong statistical model to get their results. They used a model that predicts a rapid decrease in anogenital index at low phthalate levels and smaller decreases at higher levels, a relationship that is biologically implausible.
- The overall conclusion of this study was that the authors felt that more research is needed.

The listed faults of the Swan study have led to negative reviews from NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) who examined the study and refused to consider its conclusions, stating that the results appeared to be "just noise."

Another study that has generated much media attention was conducted by Sheela Sathyanarayana and others at the University of Washington.[4] This study gives no evidence of adverse health effects from expsosure to low levels of phthalates in consumer products. Rather, the study seeks to explore the sources of infant phthalate exposure through the use of baby care products and suggests that consumers limit the "amount of infant care products used and not to apply lotions or powders unless indicated for a medical reason." While we do believe that there is potential value in the study of metabolized phthalates, we take great exception to any effort to draw unfounded conclusions that suggest human health risks are associated with the mere presence of very low levels of metabolized phthalates in urine. Sathyanarayana's report produces data that are decidedly inconclusive because of these shortcomings:

[4] This study is available at http://pediatrics.aappublications.org/cgi/reprint/121/2/e260

- The value of the study is limited in that it provides no information on the sources or levels of exposure.
- It contains unusually wide ranges of values for the phthalate metabolites listed which demonstrates that the values recorded are wildly variable and are inconclusive.
- The report mixes items such as toys and pacifiers with baby care products such as talcum powder and infant shampoo. It is disturbing that the authors of the study do not appear to know that pacifiers made in the United States are made of latex or silicone and are not made with phthalates.

Due to the many shortcomings of this particular study, we do not believe that it adds value to the existing body of research on phthalate esters and we do not believe that it should provide the basis for any specific recommendations or actions on the part of consumers or manufactures.

## EXTENSIVE SCIENTIFIC EVIDNECE SUPPORTS THE SAFETY OF BISPHENOL A IN CONSUMER PRODUCTS

Bisphenol A is a chemical building block used primarily to make polycarbonate plastic and epoxy resins. The safety of products made from these materials is supported by a 50 year safety track record of use and an equally long history of testing.

Polycarbonate is a lightweight, highly shatter-resistant plastic with optical clarity comparable to glass. Epoxy resins have an exceptional combination of toughness, chemical resistance and adhesion. The unique attributes of these materials make them ideal for use in a wide array of products, many of which improve the health and safety of consumers.

The manufacturing processes to make polycarbonate plastic and epoxy resins convert virtually all bisphenol A into the plastic or resin, leaving behind only trace levels of residual bisphenol A, typically less than 50 parts per million (0.005% by weight), in the finished materials. Consumers frequently benefit from products made from these materials, but come into contact with very little bisphenol A from use of these products.

| **Typical Products Made From Polycarbonate Plastic and Epoxy Resins** | |
|---|---|
| **Health Care**<br>• Eyeglass lenses<br>• Incubators<br>• Critical components of medical devices (e.g., kidney dialyzers, blood oxygenators, drug infusion units) | **Electronic**<br>• Digital media (CDs and DVDs)<br>• Electronic product housings (e.g., cell phones, computers)<br>• Printed circuit boards laminates |
| **Security**<br>• Blast and bullet resistant shielding<br>• Police shields<br>• Protective visors | **Sports Safety**<br>• Bicycle and football helmets<br>• Sunglasses and visors<br>• Skiing and diving goggles |
| **Automotive, Marine, and Aerospace** | **Building and Construction** |

| | |
|---|---|
| • Headlamp lenses, mirror housings and bumpers<br>• Instrument panels<br>• Primer coatings<br>• Fiber reinforced composites | • Roof, skylight and greenhouse glazing<br>• Corrosion resistant coatings for steel pipes/fittings, structural steel (e.g., bridges), concrete reinforcement bar<br>• Decorative and industrial flooring |
| **Home Appliances**<br>• Components of kitchen appliances (e.g., food processors, refrigerators)<br>• Electrical appliance housings | **Food Containers**<br>• Baby and water bottles<br>• Home food storage containers and tableware<br>• Food/beverage can coatings |

In recent years, independent government and scientific bodies worldwide have examined the scientific evidence supporting the safety of bisphenol A. In every case, these assessments support the conclusion that bisphenol A is not a risk to human health at the extremely low levels to which people might be exposed.

Each of these assessments comprehensively examined the potential reproductive and developmental toxicity of bisphenol A. Based on the weight of evidence, these assessments uniformly demonstrate that bisphenol A is not a selective reproductive or developmental toxicant. The most recent evaluations of bisphenol A are briefly summarized below along with their key conclusions regarding reproductive and developmental toxicity.

## BISPHENOL A IS DEEMED SAFE FOR USE BY THE U.S. FOOD AND DRUG ADMINISTRATION

FDA regulates the use of bisphenol A in food contact materials, such as polycarbonate used in baby bottles and water bottles, and in epoxy resins used to coat cans containing food products. The U.S. Food and Drug Administration (FDA) said in July 2007 that "FDA is unaware of any specific study in which humans exposed to BPA through any food containers experienced miscarriages, birth defects or cancer. Furthermore, human exposure levels to BPA from its use in food contact materials is in fact many orders of magnitude lower than the levels of BPA that showed no adverse effects in animal studies."

More recently (April 2008), in response to public confusion from media reports about bisphenol A, FDA formed an FDA-wide task force to review current research and new information on bisphenol A for all FDA-regulated products. FDA confirmed that it has been reviewing the emerging literature on bisphenol A on a continuous basis. FDA also confirmed that based on its ongoing review, it believes there is a large body of evidence that indicates that FDA-regulated products containing bisphenol A currently on the market are safe and that exposure levels to bisphenol A from food contact materials, including for infants and children, are below those that may cause health effects.

FDA's position is consistent with two risk assessments for BPA conducted by the European Food Safety Authority (EFSA) Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food and the Japanese National Institute of Advanced Industrial Science and Technology. Each of these documents considered the question of a possible low-dose effect and concluded that no current health risk exists for bisphenol A at the current exposure level.

FDA said in April 2008 that it is NOT recommending that anyone discontinue using products that contain bisphenol A while FDA continues its risk assessment process. See http://www.fda.gov/oc/opacom/hottopics/bpa.html.

## FDA'S CONCLUSIONS ON BPA ARE CONSISTENT WITH THOSE OF THE EUROPEAN FOOD SAFETY AUTHORITY

The European Food Safety Authority (EFSA) was established by the European Parliament in 2002 to provide the European Commission, the European Parliament and the European Member States with a sound scientific basis for legislation and policies related to food safety. Included in the scope of EFSA's work are assessments of the safety of food packaging and other materials that contact food.

In January 2007, EFSA released a comprehensive assessment of bisphenol A that was conducted by an expert panel consisting of 21 independent scientific experts from across the European Union.

[1] The assessment, which builds upon and updates an earlier assessment,[2] comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and dietary exposure of bisphenol A.

In general, the findings and conclusions of the EFSA assessment are consistent with those of the more recent CERHR evaluation (see below). The assessment established a Tolerable Daily Intake (TDI) of 50 µg/kg bw/day and concluded that "people's dietary exposure to BPA, including that of infants and children, is estimated to be well below the new TDI."

The TDI was based on the most sensitive no-effect-levels from multi-generation studies conducted in the rat and mouse (see below for more information on these studies). For both studies, the most sensitive no-effect-level was for systemic toxicity (e.g., liver effects) at 5 mg/kg bw/day. The no-effect-levels for reproductive and developmental effects in both studies were at a higher dose (50 mg/kg bw/day) than the dose at which systemic effects occurred. The EFSA panel further concluded that "low-dose effects" of bisphenol A in rodents have not been demonstrated in a robust and reproducible way.

## BISPHENOL A HAS BEEN EXTENSIVELY REVIEWED BY THE NTP CENTER FOR THE EVALUATION OF RISKS TO HUMAN REPRODUCTION

The Center for the Evaluation of Risks to Human Reproduction (CERHR) was established by the U.S. National Toxicology Program and the National Institute of Environmental Health Sciences in 1998 to serve as an environmental health resource to the public and to regulatory and health agencies. A primary function of CERHR is to assess the potential for adverse effects on reproduction and development caused by agents to which humans may be exposed. This is accomplished through rigorous evaluations of the scientific literature by independent panels of scientists.

The CERHR evaluation comprehensively reviewed the large scientific database on bisphenol A, including:

- Chemistry, use and human exposure
- General toxicology and biological effects (including metabolism and pharmacokinetics)
- Reproductive toxicity
- Developmental toxicity

To reach its conclusions, the expert panel considered the quality, quantity, and strength of the scientific evidence that exposure to bisphenol A might cause adverse effects on human reproduction and/or development of the fetus or infant. The overall findings of the expert panel evaluation were announced at a public meeting in August 2007, and the final CERHR report was released in November 2007. Subsequently, NTP released a draft "Brief" based on the CERHR report on April 14, 2008.[3]

Based on the weight of scientific evidence, the expert panel found no serious or high level concerns for adverse effects of bisphenol A on human reproduction or development. The draft NTP Brief agreed with these conclusions: "the NTP has negligible concern that the exposure of pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring," and "the NTP concurs with the conclusion of the CERHR Expert Panel on Bisphenol A that there is negligible concern that exposure to bisphenol A causes reproductive effects in non-occupationally exposed adults, and minimal concern for workers exposed to higher levels in occupational settings." For several specific potential health effects (regarding neural and behavioural effects, and effects on the prostate gland, acceleration in puberty in females, and the mammary gland), the NTP draft Brief expressed "some concern," but again no serious or high level concerns. Additional research was suggested by the NTP draft Brief, since data is inadequate to reach a firm conclusion.

## THE EUROPEAN UNION RISK ASSESSMENT SUPPORTS BISPHENOL A'S CONTINUED SAFE USE

Under the EU Existing Substances Directive, the EU conducted a comprehensive risk assessment of bisphenol A that was published in 2003.[4] An updated risk assessment is in the final stages and is expected to be published in 2008.

The EU risk assessment comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and exposure of bisphenol A. In general, the findings and conclusions of the EU risk assessment are consistent with those of the CERHR evaluation. The 2003 risk assessment established an overall no-effect-level of 50 mg/kg bw/day, which was based on the no-effect-level for reproductive and developmental effects in a multi-generation study conducted in the rat. The no-effect-level from the rat multi-generation study has subsequently been affirmed

by the results of a multi-generation study in the mouse (see below for information on both multi-generation studies). The updated risk assessment, based on the most recent scientific information, retains the overall no-effect-level of 50 mg/kg bw/day, now based on both the rat and mouse studies.

The 2003 EU risk assessment was reviewed by the Scientific Committee for Toxicity, Ecotoxicity, and the Environment (CSTEE), which is an independent scientific advisory committee to the European Commission.[5] The CSTEE agreed with the overall no-effect-level and stated that "a number of high quality studies on the reproductive and developmental effects of bisphenol A are already available and do not support low-dose effects." The CSTEE further stated that "there is no convincing evidence that low doses of bisphenol A have effects on developmental parameters in offspring…"

## THE JAPANESE NATIONAL INSTITUTE OF ADVANCED INDUSTRIAL SCIENCE AND TECHNOLOGY'S REVIEW SUPPORTS THE CONTINUED SAFE USE OF BISPHENOL A

The Japanese National Institute of Advanced Industrial Science and Technology (AIST), which is affiliated with the Japanese Ministry of Economy, Trade and Industry is Japan's largest public research organization. A comprehensive human health and environmental risk assessment on bisphenol A, conducted by scientists at AIST's Research Center for Chemical Risk Management, was published in November 2005.[6]

Based on a thorough review of the toxicological profile of bisphenol A combined with estimates of human exposure, AIST concluded that "current exposure levels of BPA will not pose any unacceptable risk to human health."

Along with systemic toxicity, a key toxicological endpoint for the AIST assessment was reproductive toxicity. Similar to the EFSA assessment, the most sensitive no-effect-level was 5 mg/kg bw/day for systemic toxicity in a multi-generation study conducted in the rat. The no-effect-level for reproductive toxicity was 50 mg/kg bw/day, at which systemic effects also occurred. The AIST assessment further concluded that findings from studies claiming reproductive effects at much lower doses were not considered to be robust in comparison to the consistent findings from studies reporting no low-dose effects.

## HEALTH CANADA'S RECENT REVIEW IS SUPPORTIVE OF CONTINUED USE OF BISPHENOL A

In April 2008, Health Canada opened a comment period on a proposal to ban polycarbonate baby bottles. This event has been the subject of some confusion in the media, because the reviewing scientists concluded "that bisphenol A exposure to newborns and infants is below levels that may pose a risk." The Canadian government nevertheless proposed moving forward with a ban on polycarbonate baby bottles based on a policy decision that the "gap between exposure and effect is not large enough." Canada also proposed to set limits on BPA in infant formula and to work with industry on alternatives for food packaging.

Canada did not suggest that parents and caregivers stop using polycarbonate bottles while the proposal is being considered. Canada did not suggest that stores stop selling polycarbonate baby bottles while the proposal is being considered. Canada did recommend that parents and caregivers continuing to use polycarbonate baby bottles "do not put boiling water in them."

## RECENT, HIGH QUALITY ANIMAL STUDIES HAVE BEEN COMPLETED ON BISPHENOL A

The effects of bisphenol A on fertility and reproductive performance have been investigated in three high quality studies in rats and mice using internationally validated guidelines (two-generation and three-generation studies in the rat, two-generation study in mice) and in a continuous breeding study in mice. Developmental toxicity studies in rats and mice have also been conducted.

- No effect on fertility was seen in the rat two-generation study at the four low-dose levels tested (0.2-200 µg/kg bw/day). In the rat three-generation study, a reduction in litter size was seen only at the top dose of 500 mg/kg bw/day, which also produced clear parental systemic toxicity (significant body weight gain reduction in both sexes and renal tubule degeneration in females). No effects on reproduction or development were seen at the five lower doses tested (1 µg/kg bw/day to 50 mg/kg bw/day) and no parental systemic effects were seen at the four lowest doses (5 mg/kg bw/day and below).
- Consistent with the rat studies, bisphenol A produced parental systemic toxicity in the mouse two-generation study at the two highest doses tested

(50 and 600 mg/kg bw/day), resulting in a NOEL of 5 mg/kg bw/day. The NOEL for reproductive and developmental effects was 50 mg/kg bw/day. No treatment related effects were seen at the four lowest doses tested (3 µg/kg bw/day to 5 mg/kg bw/day).

- In the continuous breeding study in mice, no effects on fertility were seen at 300 mg/kg bw/day. Fertility effects were only observed at doses of approximately 600 mg/kg bw/day and above, at which parental systemic toxicity was present.
- No evidence that bisphenol A is a developmental toxicant was observed in standard developmental studies in rats and mice. In rats, a maternal LOAEL and fetal NOAEL of 160 and 640 mg/kg bw/day, respectively, were identified. In mice, maternal and fetal NOAELs were 250 and 1,000 mg/kg bw/day, respectively.

Individually and collectively, these studies, these studies consistently demonstrate that bisphenol A is not a selective reproductive or developmental toxicant.

In addition, effects claimed to occur at low doses in small-scale unvalidated studies, have not been corroborated in the large-scale multi-generation studies conducted according to internationally validated guidelines. Additional detail on these studies is provided below.

Three-Generation Reproductive Toxicity Study in CD Sprague-Dawley Rats

The study followed the US EPA OPPTS test guideline 837.3800, with additional assessments beyond the guideline requirements, and was conducted under Good Laboratory Practice requirements.[7] Strengths of the study include:

- Oral route of administration, which is most relevant for human exposure
- Wide dietary dose range (6 dose groups ranging from 0.015 to 7500 ppm bisphenol A in the diet, corresponding to intakes of approximately 1µg/kg bw/day to 500 mg/kg bw/day)
- Large group size (30 animals per dose level)
- Multiple endpoints examined, including a thorough histologic evaluation

Parental systemic toxicity (a guideline requirement) was produced at the two highest doses, resulting in a NOAEL of 5 mg/kg bw/day. The NOAEL for reproductive and developmental effects was 50 mg/kg bw/day.

Two-Generation Reproductive Toxicity Study in CD-1 Swiss Mice

The study followed the internationally accepted OECD 416 test guideline, with additional assessments beyond the guideline, and was conducted under Good Laboratory Practice requirements.[8] The study was preceded by a full two-generation reproductive toxicity study on 17β-estradiol, which was then also used as a positive control in the bisphenol A study. Strengths of the study include:

- Oral route of administration, which is most relevant for human exposure
- Wide dietary dose range (6 dose groups ranging from 0.018 to 3500 ppm bisphenol A in the diet, corresponding to intakes of approximately 3µg/kg bw/day to 600 mg/kg bw/day)
- Large group size (28 animals per dose level)
- Multiple endpoints examined, including a thorough histologic evaluation

In addition, maternal and paternal toxicity (a guideline requirement) was produced at the two highest doses, additional F1 male offspring were retained for evaluation concurrent with F1 parental males, a positive control was used to demonstrate that the test system was responsive to a known estrogen, and two negative control groups were used to increase the baseline historical database in mice and to define the intrinsic variability in endpoints of interest.

Consistent with the three-generation study in rats, systemic toxicity was identified at the two highest doses, resulting in a no observed effect level (NOEL) of 5 mg/kg bw/day. The NOEL for reproductive and development effects was 50 mg/kg bw/day. Also consistent with the three-generation rat study, no treatment-related effects were found at doses ranging from 3µg/kg bw/day to 5 mg/kg bw/day and the study did not corroborate effects claimed to occur in this low dose range in small-scale studies.

Two-Generation Reproductive Toxicity Study in CD Sprague-Dawley Rats

In a third comprehensive study, bisphenol A has been tested in a two-generation reproductive toxicity study in CD Sprague-Dawley rats.[9] This study,

which focused on low doses, followed the internationally accepted OECD 416 test guideline and was conducted under Good Laboratory Practice requirements. Strengths of the study include:

- Oral route of administration
- Large group size (25 animals per dose level)
- Wide variety of hormonally sensitive endpoints examined, including behavioral measurements

Consistent with the three-generation rat study and the two-generation mouse study, no treatment-related effects were found in the low-dose range from 0.2 to 200 µg/kg bw/day and the study did not corroborate effects claimed to occur in this low dose range in small-scale studies.

National Toxicology Program Continuous Breeding Study in Mice

Bisphenol A was administered in the diet during a one-week pre-mating period and a 14-week mating trial to groups of twenty male and female CD1 mice (F0 generation) at concentrations of 0, 0.25, 0.5 or 1.0%; daily intakes of bisphenol A are estimated to have been 0, 300, 600 and 1200 mg/kg bw/day in males, and 0, 325, 650 and 1300 mg/kg bw/day in females.[10] In the continuous breeding phase, a statistically significant decrease in maternal body weight was observed after each litter (between 6 and 9%), at the top dose, on postnatal day 0 compared to controls. At study termination, a small but statistically significant decrease in body weight (4%) was observed in treated females compared to controls.

A subsequent one generation study to further evaluate parental toxicity of bisphenol A to CD1 mice observed significant parental toxicity at doses of 650 or 1300 mg/kg bw/day.[11] Key evidence of parental systemic toxicity was increased liver and kidney weights with hepatocellular hypertrophy and renal tubule degeneration/regeneration, reduced body weights and body weight gain. In the continuous breeding study, a statistically significant decrease compared to controls was observed in the number of litters produced per pair (4.5 and 4.7 compared to 5.0 for controls), litter size (6.5 and 9.8 compared to 12.2 for controls) and the number of live pups per litter (6.3 and 9.7 compared to 12.1 for controls) in the high and mid-dose group. No effects on fertility were observed in the low-dose group. A statistically significant decrease in litter size (controls: 11.4, treated males: 9.1, treated females: 5.9) and number of live pups per litter (controls: 11.3,

treated males: 8.4, treated females: 5.5) were observed in the cross-over mating. In the continuous breeding phase, a statistically significant decrease in live pup weight (6%) on postnatal day 0 was observed in females at the top dose after adjustment for litter size, including live and still births. In the continuous breeding phase a small but statistically significant decrease in body weight gain (4%) was only observed in treated females at study termination. No effect was observed on the sex ratio in the F1 generation. In the F1 litters used in the cross-over breeding experiment, post natal (day 0) pup weights were significantly increased in males (9-11%) and in females (8-10%) in the mid- and high-dose.

This study, conducted at high doses, is superseded by the more recent two generation study in mice.

National Toxicology Program Developmental Toxicity Study in Mice

Bisphenol A has been tested for developmental toxicity in a NTP study using CD-1 mice.[12] Two tests were performed and as the same signs of maternal toxicity were observed in both tests the data were combined. Groups of 29-34 time-mated female mice were gavaged with 0, 500, 750, 1000 or 1250 mg/kg bw/day in corn oil on days 6 to 15 of gestation. Animals were sacrificed on day 17 of gestation and the fetuses were subjected to routine external, visceral and skeletal examinations. Data were also provided on the additional dose level of 250 mg/kg bw/day, which was used only in the first test. Some maternal deaths were observed at doses of 750 mg/kg bw/day and above and a decrease in maternal body weight gain of 4-10% and 32-43%, for both the treatment and gestation period was observed at 1,000 and 1,250 mg/kg bw/day, respectively. Other significant signs of maternal toxicity were observed at 500, 750, 1000 or 1250 mg/kg bw/day as well as a dose-related statistically significant increase in mean relative liver weight (9-26%) was observed in dams in all bisphenol A treatment groups as compared to controls. At 1250 mg/kg bw/day a statistically significant increase was observed in % resorptions per litter (40% as compared to 14% in controls). A dose-related decrease in mean fetal body weight per litter was observed in the bisphenol A treated groups that was statistically significant at 1,250 mg/kg bw/day when compared to the control value; 1%, 1%, 9% and 14% at 500, 750, 1,000 and 1,250 mg/kg bw/day, respectively. No statistically significant effect was observed on the number of implantation sites per dam, the number of live fetuses per litter and the sex ratio. Bisphenol A administration had no significant effect on the % of fetuses malformed per litter or the % of litters with malformations. Overall, a significant

increase in resorptions and decrease in fetal body weight was observed only at 1,250 mg/kg bw/day in the presence of severe maternal toxicity.

National Toxicology Program Developmental Toxicity Study in Rats

Bisphenol A was studied for developmental toxicity potential in a NTP study.[13] In the main study, two trials were performed and the data from both tests were combined. In total, groups of 27-29 time-mated CD rats were gavaged with 0, 160, 320, 640 or 1,280 mg/kg bisphenol A in corn oil on days 6 to 15 of gestation. Animals were sacrificed on day 20 of gestation and the fetuses were subjected to routine external, visceral and skeletal examination. At 1,280 mg/kg, deaths were observed in 7/27 females and because of this high mortality rate, the top dose group was not included in statistical analyses. Compared to controls, a statistically significant decrease in mean maternal body weight gain was observed in dams at all dose levels for the treatment period (35-54%) and the gestation period (11-14%). No effect was observed on gravid uterine weights. When maternal body weight gain was corrected for gravid uterine weight a statistically significant decrease was still apparent at all dose levels (26-34%). Pregnancy rates were not affected by treatment with bisphenol A, nor was there any effect on the number of implantation sites per litter, % resorptions per litter, number of live fetuses per litter, sex ratio, mean fetal body weight per litter, % fetuses malformed per litter and % litters with malformed fetuses. In conclusion, this study provides no evidence of developmental toxicity in the rat at exposure levels which are toxic to the mother. A maternal NOEL could not be identified; instead a LOAEL of 160 mg/kg was identified for clinical signs of toxicity and a statistically significant decrease (26%) in body weight gain. No fetal effects were seen at the highest dose level evaluated, 640 mg/kg.

## "LOW-DOSE" STUDIES ARE UNVALIDATED

Although bisphenol A has been shown to have some weak "estrogen-like" activity in a number of in vitro and in vivo screening assays, molecular biology studies[14] have demonstrated that bisphenol A does not act as a weak estrogen mimic but exhibits a distinct mechanism of action from estradiol at the estrogen receptor. Nevertheless, the potency of this activity in screening assays generally ranges from 3 to 5 orders of magnitude less than that of estradiol.

It should also be noted that many of the studies investigating endocrine modulating activity are essentially screening tests and many employ experimental protocols that have not been validated. This information in conjunction with the known extensive metabolism of bisphenol A to non-estrogenic metabolites (see below) provides a scientific basis for the lack of toxicological effects at low doses in the multi-generation studies described above. Effects claimed to occur at low doses in small-scale unvalidated studies have not been corroborated in the large-scale multi-generation studies conducted according to internationally validated guidelines.

The small-scale unvalidated studies have been evaluated in the comprehensive assessments described above. Each of these assessments applied a "weight-of-evidence" approach to evaluate the body of information available for bisphenol A. Each assessment relied on the results of the two- and three-generation studies described above for its overall conclusion.

## METABOLISM AND PHARMACOKINETICS DATA SUPPORTS RESULTS FROM ANIMAL STUDIES

The potential for a substance to cause reproductive or developmental toxicity is substantially influenced by metabolism and pharmacokinetics. These parameters have been very well characterized for bisphenol A in numerous animal studies (i.e., rodents and primates) and in several human volunteer studies.

Overall, these studies indicate that bisphenol A has a low potential to cause adverse health effects in humans and, in particular, effects mediated by an estrogenic mode of action. Key findings from these studies are summarized below:

- **Humans Efficiently Metabolize and Eliminate Bisphenol A from the Body**
  Human volunteer studies confirm that bisphenol A is efficiently metabolized to a glucuronide conjugate after oral exposure.[15,16,17] Studies in animals and with isolated liver cells have shown that this metabolic process occurs in the intestinal wall[18] and in the liver,[19,20,21,22] both of which must be crossed before bisphenol A can enter into circulation in the body after oral exposure.

  In the first human study, volunteers were treated with a single 5 mg oral dose of bisphenol A per person, which is approximately 1000 times greater

than a typical daily intake of bisphenol A (see Section 6 below). No parent bisphenol A was found in blood at any time point and all bisphenol A was excreted in urine as the glucuronide. The elimination half-life for the glucuronide conjugate was approximately 4 hours, which means that any bisphenol A to which people are exposed should virtually all be eliminated from the body within approximately 24 hours.

- **Bisphenol A Has Low Bioavailability and Does Not Accumulate in the Body**
  The human volunteer studies confirm that bisphenol A has very low bioavailability (i.e., very little parent bisphenol A will reach target tissues) after oral exposure. The rapid elimination of bisphenol A indicates that bisphenol A has very low potential (if any) to bioaccumulate in the body.

  Low bioavailability, efficient metabolism of bisphenol to the glucuronide, and low potential to bioaccumulate have also been demonstrated in numerous studies on laboratory animals, some of which are cited here.[23,24,25,26,27,28,29] Included are studies that demonstrate that metabolism of bisphenol A is not altered during pregnancy[30] and that neonatal animals also efficiently metabolize bisphenol A from an early age in neonatal life.[31]

- **Bisphenol A Metabolites are Not Estrogenic**
  The primary metabolite of bisphenol A, the glucuronide, has been shown to exhibit no estrogenic activity.[32] The bisphenol A sulfate metabolite, which may be present at lower levels, has also been shown to exhibit no estrogenic activity.[33] These studies indicate that bisphenol A is not likely to cause estrogenic effects since the metabolites of bisphenol A that enter the body have no known biological activity and, in particular, have no estrogenic activity.

## BISPHENOL A PRESENTS VERY LOW POTENTIAL FOR HUMAN EXPOSURE

Numerous studies have been conducted to directly measure human exposure to bisphenol A by urinary biomonitoring and to indirectly estimate human exposure by analysis of potential sources of exposure. These data consistently indicate that human exposure to bisphenol A is essentially all through the diet and is extremely low. Typical human exposure to bisphenol A is less than 0.1 μg/kg bw/day. Key findings from these studies are summarized below:

- **Biomonitoring Studies Confirm Extremely Low Human Exposure**
  Since the glucuronide metabolite of bisphenol A is rapidly and completely eliminated into human urine, human exposure can readily be estimated by urinary biomonitoring for bisphenol A (after hydrolysis of conjugates). Numerous studies conducted worldwide indicate that typical human exposure to bisphenol A is less than 0.1 µg/kg bw/day.

  The largest study was conducted by the US Centers for Disease Control and Prevention as part of their NHANES 2003-2004 program.[34] This study reported urinary bisphenol A data for more than 2500 individuals ranging in age from 6-85. Due to the study design, the data is representative of the US population. In this study, the median concentration of bisphenol A in urine (after hydrolysis) was 2.8 ng/ml. Based on this data, the typical daily intake of bisphenol A for the population is estimated to be approximately 0.05 µg/kg bw/day.

  Many smaller-scale studies from Japan[35,36,37,38,39], Korea,[40,41] Europe,[42] and the US[43,44,45,46,47,48,49] have reported similar results. Included are two studies in which urine samples were collected over 24-hour periods.[50,51]

- **Potential Exposure From Consumer Products is Very Low**
  Consumer products made from polycarbonate plastic or epoxy resins contain only trace levels of bisphenol A, typically less than 50 parts per million (0.005% by weight), which limits potential exposure to bisphenol A from use of products. Human exposure to bisphenol A is essentially all through the diet[52] and numerous studies have been conducted to examine the potential for bisphenol A to migrate from polycarbonate plastic or epoxy resins into a food or beverage. Of particular interest are the many studies on polycarbonate baby bottles[53,54,55,56,57,58] and canned foods and beverages.[59]

  Calculated human exposure estimates based on measured migration data combined with consumption patterns,[60] are generally consistent with exposure estimates directly measured by biomonitoring. Both confirm that human exposure to bisphenol A from all sources, including from use of consumer products, is extremely low.

- **Exposure to Bisphenol A Is Within Government-Set Safe Limits**
  The European Food Safety Authority recently established a Tolerable Daily Intake for bisphenol A of 50 µg/kg bw/day based on an up-to-date scientific review. This value is identical to the Reference Dose set by the US Environmental Protection Agency.[61] The typical daily intake of bisphenol A is approximately 1,000 times lower than these acceptable levels and poses no known risks to human health.

## CONCLUSION

From a toxicological perspective, BPA and phthalates are among the most well defined chemicals on earth. They have been the subject of hundreds of studies in lab animals and numerous government-sponsored assessments. Accordingly, based on the science and the use patterns for these compounds, no restriction on their uses in current applications is warranted at this time.

[1] European Food Safety Authority. January 29, 2007. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) related to 2,2-BIS(4-HYDROXYPHENYL)PROPANE. A summary report and full report are available at http://www.efsa.europa.eu/en/science/afc/afc_opinions/bisphenol_a.html.

[2] European Commission. April 17, 2002. Opinion of the Scientific Committee on Food on Bisphenol A. Available at http://ec.europa.eu/food/fs/sc/scf/out128_en.pdf.

[3] Information on the CERHR evaluation, including the April 14 NTP draft brief, is available at http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.html. The final report will also be posted on this site.

[4] European Union Risk Assessment Report – 4,4'-isopropylidenediphenol (Bisphenol-A). 2003. Available at http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/SUMMARY/bisphenolasum325.pdf (summary) and http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/bisphenolareport325.pdf (full report).

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